Interventional Pain Medicine 1 (2022) 100106

Contents lists available at ScienceDirect

Interventional Pain Medicine

journal homepage: www.journals.elsevier.com/interventional-pain-medicine

Intra-flexor retinaculum steroid injection in elderly patients with carpal tunnel syndrome: A randomized clinical trial

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ARTICLE INFO

Keywords:
Aged
Carpal tunel syndrome
Injection
Steroids
Ultrasonography
Surgery
Pain
Wrist

ABSTRACT

Introduction: The efficacy of ultrasonography-guided intra-flexor retinaculum corticosteroid injection is compared to within-carpal tunnel steroid injection, for the treatment of elderly patients with carpal tunnel syndrome (CTS).
Material & methods: In this prospective, double-blind, randomized trial, the elderly patients with CTS are allocated 1:1 into the two treatment groups. Subjects and assessors remained blinded to group allocation throughout the trial. All patients received 40 mg triamcinolone (1 mL) plus 1 mL of 2% lidocaine, either fenestrated in the flexor retinaculum (group 1) or injected within the carpal tunnel between the flexor retinaculum and median nerve (group 2). Patients were instructed to use a wrist splint for two weeks post-treatment. Symptom severity, grip, electrodiagnostic indices, and ultrasonographic features were measured at baseline and 6-weeks thereafter. The primary outcomes were median nerve distal motor and sensory latencies, and those secondary outcomes were Boston Carpal Tunnel Questionnaire (BCTQ) scores, visual analog scale (VAS) pain scores, and the median nerve inlet cross-sectional area (CSA).
Results: Of 92 individuals screened, 50 eligible participants were randomized, all of whom completed the study and were included in the analysis. Patients receiving the intra-flexor retinaculum injection demonstrated significantly greater improvements in their total BCTQ score ($p = 0.023$), VAS score ($p = 0.026$), and inlet CSA ($p = 0.004$), while the electrodiagnostic indices and the grip scale did not differ between groups.
Conclusion: The intra-flexor retinaculum corticosteroid injection can provide better functional recovery and symptom reduction for elderly patients with CTS, compared to the within-carpal tunnel corticosteroid injection.

1. Introduction

There are many available therapeutic options with demonstrated clinical efficacy for hand pain caused by carpal tunnel syndrome (CTS), including both surgical and nonsurgical interventions [1]. Carpal tunnel release surgery, which involves transverse carpal ligament transsection to reduce pressure on the median nerve and tendons within the carpal tunnel, is considered among the most effective long-term treatments for patients with severe or persistent symptoms [2]. For instance, a systematic review concluded that surgical carpal tunnel release has superior benefits for symptom reduction and function improvement at 6 and 12 months post-treatment, compared to various conservative treatments [3,4]. However, this surgery also carries the risk of some side-effects, including severe neurovascular complications, tendonal injuries, infections, persistent skin pain, and skin neuromas which are rare, but happen nonetheless. The use of anesthesia for certain populations, including the elderly, are relative contra-indicated. With that in mind, less invasive approaches seem appropriate in high risk populations, however there is no consensus about them and more research in that field is necessary [5,6]. Corticosteroid injection is widely used to relieve motor and sensory symptoms associated with nerve inflammation, including symptoms of CTS. Although generally viewed as a benign modality, CTS injections may result in iatrogenic lesions to the median nerve and corticosteroid-induced hypopigmentation [4]. Additionally, soft tissue

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https://doi.org/10.1016/j.inpm.2022.100106
Received 25 January 2022; Received in revised form 21 May 2022; Accepted 23 May 2022

atrophy has been reported in up to 40% of patients receiving the corticosteroid injection [7], with specific incidence depending on patient characteristics, the corticosteroid injected, and the injection technique itself [4,8]. On the other hand, steroids have some cyto-toxic effects on fibroblasts and tenocytes [9] that can be found in the flexor retinaculum of at least some CTS patients [10,11]. It was speculated that the atrophying and cyto-toxic effect of the corticosteroid injection directly within the flexor retinaculum could decrease pressure on the median nerve, thereby providing the benefits of surgical decompression, with fewer devastating complications comparing to surgery and blind with in canal injection, as well as less subcutaneous atrophying compared to soft tissue steroid injection [5,11–16].

Here, an ultrasonography-guided intra-flexor retinaculum corticosteroid injection technique is described, alongside the results of a randomized trial comparing its clinical efficacy to within-carpal tunnel injection near the nerve for elderly patients with CTS.

2. Methods

2.1. Setting and design

The current prospective, double-blind, parallel, randomized trial was conducted on patients sixty years and older referred to the Physical Medicine and Rehabilitation Clinic of the University Hospital, Tehran, Iran, from September 2018 to February 2020.

Included were clinically diagnosed CTS patients who were confirmed with electrodiagnosis (EDX) for moderate CTS. For the clinical diagnosis, the American Academy of Orthopedic Surgeons Clinical Practice Guideline recommendations [17] were followed, and only one physician evaluated and examined the patients. He took a comprehensive history of present illnesses, including the pace activities that induced patient symptoms and comorbidities. He also examined patients thoroughly for CTS with standard sensory, manual muscle testing and provocative tests, such as Phalen, and the compression and spurling tests for alternative cervica root lesion diagnoses. For the EDX, nerve conduction studies (NCSs) and electromyography (EMG) were performed by just one physician with more than 15 years of experience. The American Association of Neuromuscular and Electrodiagnostic Medicine Guideline was the framework of the CTS diagnosis [18]. Only the dominant hand of the patient with bilateral CTS was included in the study after CTS confirmation, and for that, the NCS reference value by Dumitru et al. were used [19].

The exclusion criteria were: 1) severe weakness, requiring carpal tunnel release; 2) a previous history of CTS treatment or injection; 3) corticosteroid allergies or contraindication; 4) co-morbidities such as diabetes mellitus, rheumatoid arthritis, thyroid dysfunction, or any severe heart diseases and 5) the presence of concomitant neuropathies such as polyneuropathy, proximal median or ulnar neuropathy, plexopathy, mononeuritis multiplex, and cervical radiculopathy.

Recruited patients were randomized to study or control groups at a 1:1 ratio using a computer-generated list distributed by an investigator not involved in other aspects of patient evaluation or treatment. The results are reported in strict accordance with CONSORT guidelines.

An Esaote ultrasound system (MyLab™-25; Esaote, Genoa, Italy) with a 10–18 MHz multidimensional linear-array transducer was used for all ultrasound evaluations and injection guidance. Subjects lay supine with the forearm supinated and the wrist turned inward with mild dorsiflexion on a rolled towel. Then the probe was placed on the patients' skin at the level of the pisiform bone in short axis parallel to the transverse plane of the upper limb to find the carpal tunnel and median nerve, rotated to be perpendicular to the above mentioned plan to get the whole course of the median nerve for injections. The skin was then prepared and a 22-gauge needle was used for injection.

Patients in the intervention group (group I) received a single injection of 40 mg triamcinolone (1 mL) plus 1 mL of 2% lidocaine within the flexor retinaculum over the median nerve under ultrasound guidance. The needle was advanced incrementally from distal to proximal and in a fanwise manner, as the practitioner gradually injected the entire 2-mL volume before reaching the proximal extent of the flexor retinaculum. Patients in the control group (group II) also received a single injection of 40 mg triamcinolone (1 mL) plus 1 mL of 2% lidocaine under ultrasound guidance, but between the flexor retinaculum and median nerve.

All patients were instructed to wear a wrist splint for at least two weeks following injections, and were advised not to use any other therapy for CTS. Subjects and the analyzer remained blinded to group allocation throughout the trial.

2.2. Measurements

Age, sex, and dominant versus nondominant hand involvement were recorded as demographic factors. Pain severity was assessed at baseline and at 6 weeks post-injection by a visual analog scale (VAS) and grip strength via hand dynamometry. A nerve conduction study (NCS) was performed to confirm the CTS diagnosis and evaluate the treatment efficacy as described, with median nerve distal motor latency (median DML) and median nerve sensory nerve action potential (median SNAP) recorded as the primary outcomes (16). The 19-item Boston Carpal Tunnel Questionnaire (BCTQ), comprised of an 11-item Symptom Severity Scale and 8-item Functional Status Scale was completed by each patient at baseline and at follow-up. The median nerve inlet cross-sectional area (inlet CSA), the most sensitive and specific sonographic marker for diagnosing CTS, was measured as the sonographic outcome parameter. Although we did not measure the thickness of median nerve or in canal pressure, the inlet CSA is a sensitive index that represents the pressure in the canal indirectly [20,21]. However, in one of the patients measured, the flexor retinaculum thickness was markedly reduced post-treatment in the intra-flexor retinaculum steroid injection group (Fig. 2).

Patients were also asked about adverse effects at a follow-up review.

2.3. Ethical issues and registration

This study was designed according to the ethical principles of the Helsinki Declaration and was approved by the Ethics Review Board of the PM&R research center, Shahid Beheshti University of Medical Sciences (No. 34–13). The trial was also registered at IRCT.ir, as an addendum to our previous work [22] (Identifier Number: IRCT2014020416485N1). All patients were informed of study objectives, various CTS treatment options, and the potential adverse effects of local steroid injection, including hypopigmentation, subcutaneous tissue atrophy, and possible median nerve injury. Written informed consent was obtained from all participants before enrollment.

2.4. Sample size calculation

A sample size of 21 subjects per group was deemed sufficient, assuming a total success rate of 70% for local steroid injection according to responses "worse/no effect," versus "slightly better/much better/cured," and setting an absolute precision of 0.2, statistical power of 0.8, and significance level of 0.05.

2.5. Statistical analysis

All trial data were analyzed using IBM SPSS Statistics, Version 19.0 (SPSS Inc., Chicago, IL, USA). Treatment outcomes were assessed based on the intent-to-treat principle, so analyses included all randomized participants. Data distribution was first assessed by applying the Kolmogorov–Smirnov test with $\alpha = 0.05$ considered significant (violating normality). Pre- and post-treatment values were compared for each subject using paired-sample t-tests. Baseline characteristics and primary outcome measures were compared between groups using independent-samples t-tests (for continuous variable) or Chi-square tests (for

categorical variables).

2.6. Data availability

All data points are available if any further analysis is required.

3. Results

Fig. 1 presents the flowchart for recruitment, randomization, and treatment. Of 92 individuals screened, fifty were deemed eligible and randomized to one of the two treatment groups. All randomized subjects completed the study and were included in the analyses. The two treatment groups were relatively well matched for age, sex ratio, and the ratio of dominant to nondominant hand involvement (Table 1).

Both groups demonstrated significant improvements in mean VAS score, mean total BCTQ score, median DML, median SNAP, mean grip strength, and mean inlet CSA at the 6-week follow-up compared to baseline (all $p < 0.05$) (Table 2). However, the intra-flexor retinaculum steroid injection group demonstrated greater improvements in BCTQ, VAS, and ultrasonographic measures (all $p < 0.05$) (Table 2), while improvements in electrodiagnostic and grip scales did not differ between treatment groups. The intra-flexor retinaculum steroid injection group was also greatly improved in BCTQ functional status scale scores ($p = 0.016$). In addition, the final BCTQ symptom severity scale score was lower in the intra-flexor retinaculum steroid injection group, but the inter-group difference in change from baseline did not reach statistical significance ($p = 0.261$).

4. Discussion

CTS is a major cause of chronic disability among working-age adults, and despite high global prevalence and treatment costs, there is still no consensus on the optimal treatment regimen [23–25]. It is therefore critical to identify more effective and less costly treatment strategies. Early treatments are particularly vital for elderly patients with CTS, due to the enhanced susceptibility of this group to irreversible peripheral nerve damage, and generally greater disease severity [26]. Demonstrated in this research is how ultrasonography-guided intra-flexor retinaculum corticosteroid injection can achieve superior functional outcomes and symptom reduction compared to within-carpal tunnel corticosteroid injection for elderly patients with CTS. However, there is no well-defined age cut-off for predicting these increased risks [25] as the gradual age-associated decline in peripheral nerve function is highly dependent on diverse genetic and environmental factors. In this study, 50 years was set as the cut-off age based on factors described in a previous study on steroid injection for elderly patients with CTS [22]. Nonetheless, the findings suggest that this new injection technique is broadly effective for older patients with CTS.

The current American Academy of Orthopedic Surgeons (AAOS) Practice Guidelines recommend either local corticosteroid injection or surgical release as initial CTS treatment [17,27], but the comparative benefits are still debated. Milone et al. concluded that prompt surgical release is the costliest treatment option [28], but others have advocated for immediate surgical release as a more cost effective treatment [29,30] due to the medical and non-medical costs of prolonged conservative management. Patients desiring more rapid and permanent symptom

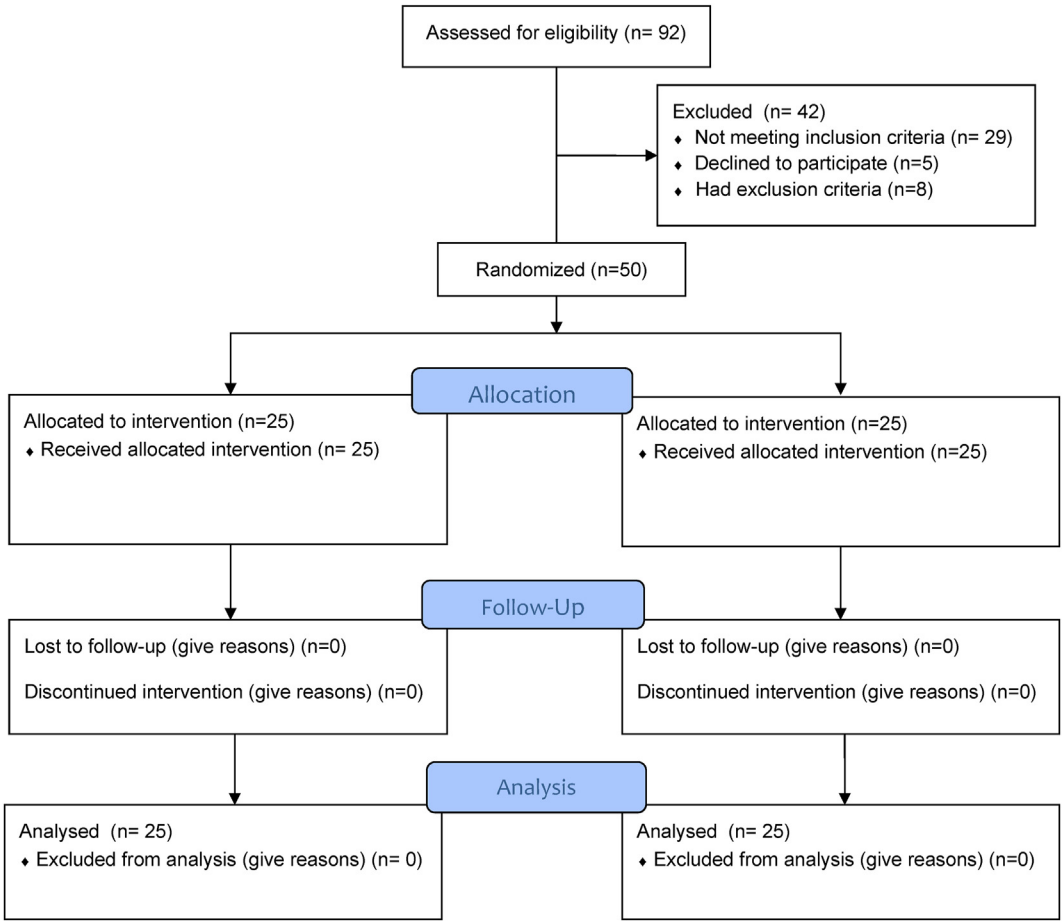

Fig. 1. Study flowchart.

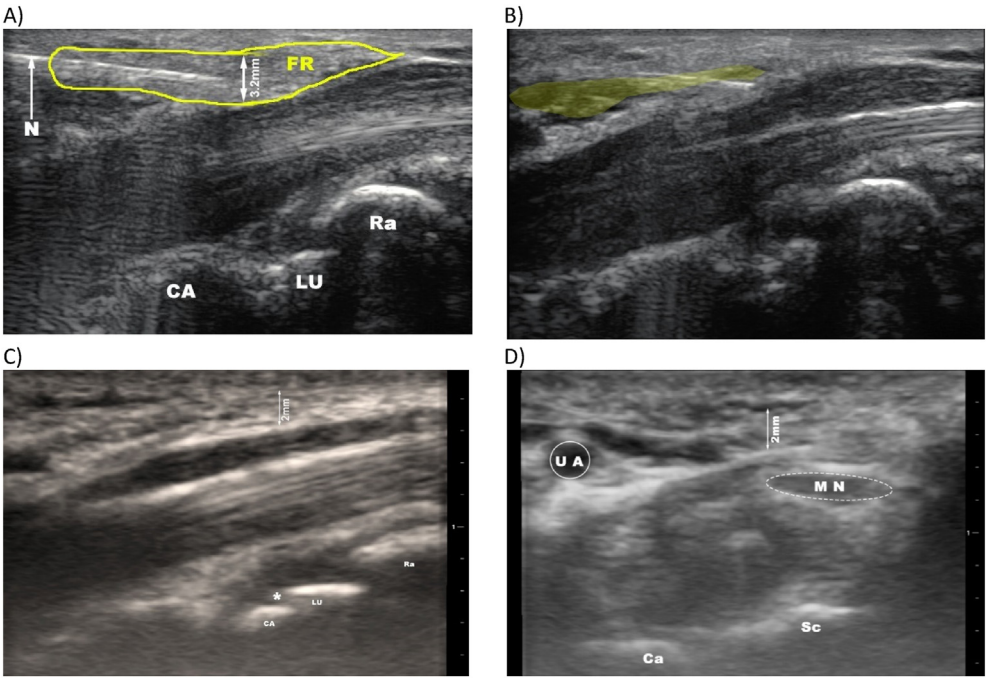

Fig. 2. Sonographic assessment of the carpal tunnel condition, following the intra-flexor retinaculum.

Table 1
Participant demographics.

	Group I	Group II	P-value
Age	65.72 ± 5.5	64 ± 4.16	0.387
Female/male ratio	68%/32%	80%/20%	0.333
Dominant/nondominant hand involvement	92%/8%	80%/20%	0.221

relief may be willing to accept higher direct costs of surgery. In contrast, local corticosteroid injection may reduce the need for further surgery in some cases [28], and certain patients may prefer to avoid surgery. Thus, patient preference should be considered in CTS management.

Initial treatment efficacy and duration are obviously critical factors for treatment guidance, but potential treatment benefits must be weighed against possible complications. T\

he AAOS Practice Guideline states that CTS surgical treatments have a very good outcome up to 12 months. Documented also is str.

\ong evidence for improved patient-reported conditions following the corticosteroid injection [31], although the duration of these benefits appears inconsistent across studies. Shi et al. presented low-to moderate-quality evidence for no statistically significant differences in functional or symptom outcomes between surgical and nonsurgical interventions at 1 and 3 months post-treatment [32], while surgical interventions demonstrated low to moderate superiority for improved functional status, reduced symptom severity, and better distal sensory latency at 6 months. However, these benefits were reduced at 12 months post-treatment [32]. Thus, numerous factors, such as patient values and preferences, predicted magnitude and rate of recovery, comorbidities, presenting symptoms, degree of nerve damage, and complication risks must be considered. Further, some practitioners suggest an initial trial of conservative management [25,31,32], as satisfactory outcomes may mitigate the need for surgical intervention, while others have declared that the optimal strategy is an informed choice based both on the physician's recommendation and the patient's own preference (Milone et al., 2019).

In this report, a new approach to the management of elderly people with CTS was evaluated, involving corticosteroid injection directly into the flexor retinaculum. Based on the known atrophying effect of corticosteroids, it was speculated that this treatment would induce some degree of transverse carpal ligament release, thus achieving the benefits of both surgical intervention (e.g. effective reduction of pressure on the nerve based on previous studies [20,21]) and conservative management (e.g. low cost and low complications). This approach also does not require extended time off work. Concomitantly, because of its release-like effect secondary to transverse carpal ligament atrophy, intra-flexor retinaculum injections can achieve longer-term benefits. Although flexor retinaculum is of a relatively superficial structure, there was no subcutaneous fat atrophy seen in the patients, perhaps due to flexor retinaculum injectant retention, as showed in previous studies [11, 33]. So, it may reduce the patient psycho-social burden and improve cosmetic outcome, thereby adding to patient satisfaction. Further, the new technique achieved greater improvements in ultrasonographic measures, function, and symptom severity compared to within-tunnel corticosteroid injection.

Local soft tissue atrophy may occur in up to 40% of local steroid injections [7] depending on patient, drug, and procedural characteristics [4,34], which in this case are considered confounding factors as they may directly impact therapeutic efficacy. For instance, there is marked lipoatrophy predominance after steroid injection in females with more subcutaneous fat tissue. Low-solubility steroids such as triamcinolone acetonide have superior atrophying effects compared to high-solubility agents like dexamethasone. As solubility is inversely related to the duration of action, low-solubility agents also show a longer duration of action concomitant with greater atrophying (Papadopoulos & Edison, 2009; Sawaizumi et al., 2007). It has been postulated as well that procedure frequency and the injection depth can enhance the duration of action and atrophy [4]. Moreover, some studies have found that a better focused drug delivery (i.e., minimizing the spread to the surrounding soft tissues) can reduce atrophy. Therefore, higher-gauge needles, a larger injection volume, a higher drug concentration, and multiple injection sites may increase soft tissue atrophy [4] and therapeutic efficacy. The interval between injections relative to the time course of atrophy may also influence the final outcome. Ultimately, however, the duration of clinical efficacy may be limited as soft tissue changes are usually reversible, generally appearing in 2 weeks–4 months post-injection and regressing spontaneously over 6–30 months [4,35].

Table 2
Group comparison of outcome measures.

Outcome		Baseline	Six-week follow-up	Paired samples *t*-test	independent-samples *t*-test
VAS	Group I	7.04 (2.65)	2.72 (1.67)	**<0.001***	**0.026***
Mean (SD)	Group II	7.12 (2.33)	4.44 (1.50)	**<0.001***	
Median DML	Group I	4.84 (0.99)	4.69 (0.82)	0.043	0.094
Mean (SD)	Group II	4.78 (0.70)	4.46 (0.67)	**<0.001***	
Median SNAP	Group I	4.48 (0.68)	4.38 (0.85)	**0.012***	0.526
Mean (SD)	Group II	4.38 (0.55)	4.09 (0.46)	**0.001***	
BCTQ	Group I	52.2 (12.79)	28.08 (10.46)	**<0.001***	**0.023***
Mean (SD)	Group II	57.72 (10.28)	41.24 (9.37)	<0.001*	
BCTQ symptom severity scale	Group I	29.88 (7.31)	15.8 (6.06)	**<0.001***	0.261
Mean (SD)	Group II	34.92 (9.41)	23.44 (5.37)	**<0.001***	
BCTQ functional status scale	Group I	22.32 (5.49)	12.28 (4.41)	**<0.001***	**0.016***
Mean (SD)	Group II	22.8 (8.1)	17.8 (4.02)	**0.009***	
Inlet CSA	Group I	12.08 (2.66)	9.44 (2.35)	**<0.001***	**0.004***
Mean (SD)	Group II	12.4 (1.82)	11.82 (1.26)	**0.007***	
Grip	Group I	23.52 (8.63)	28.52 (7.68)	**<0.001***	0.149
Mean (SD)	Group II	22.95 (7.44)	30.26 (10.13)	**<0.001***	

VAS: visual analog scale; DML: distal motor latency; SNAP: sensory nerve action potential; BCTQ: Boston carpal tunnel questionnaire; CSA: cross-sectional area; SD: standard deviation.
*Statistically significant.

Strengths of the current randomized controlled trials (RCT) include the application of a comprehensive approach to CTS diagnosis, strict adherence to RCT design standards in drafting and implementing study steps, adherence to the CONSORT statement for reporting, the use of widely validated and quantitative outcome measures such as the BCTQ, NCSs, ultrasound parameters, and double-blinding throughout the trial. Furthermore, treatment groups were well-matched demographically and received the same drugs. Finally, the steroid treatment was chosen according to literature-based knowledge of steroid-induced atrophy. This study did not include a true placebo group, an untreated/sham control group, or a surgical group for comparison. A direct atrophying effect on the flexor retinaculum by direct FR thickness measurement was not confirmed; however, the inlet CSA is a sensitive index that represents the pressure in the canal indirectly [20,21]. Moreover, patients were followed-up at 6 weeks, so longer-term benefits of this new treatment remain unknown and should be evaluated. Additionally, the effects of atrophy-related confounding factors, such as patient traits and specific corticosteroid characteristics, were not evaluated. Therefore, methodologically high-power studies including a control group and a surgery group, assessing atrophy-related confounding factors as well as atrophy incidence, reversibility, extent, dependence on patient traits and treatment parameters (age, drug concentration, site, timing, single vs. multiple injections), and association with primary outcomes are needed to confirm the broad therapeutic efficacy and safety of this method.

5. Conclusion

This study demonstrates that intra-flexor retinaculum corticosteroid injections can provide superior clinical results compared to within-carpal tunnel corticosteroid injections for elderly patients with CTS.

Disclosure

The authors report no conflicts of interest in this work.

Funding

This research did not receive grant from funding agencies in the public, commercial, or not-for-profit sectors.

Meeting presentation

NA.

Financial support

No financial support by any governmental, private or NJO institute or corporations.

Proprietary interest statement

Non of the authors has any property interest, no conflicts of interest, no competing interest in this work.

Précis

Steroid injection in flexor-retinacullum had better outcomes comparing to intra carpal tunnel injection.

Authors contribution statement

Reza S. Roghani: Conceptualization, Methodology, Investigation, Data curation, Writing-Original draft, Project administration, Sam Kara: Data curation, Writing-Review &editing, Mohammad J. Taheri: Investigation, Resource, Writing-Original draft, Faeze Gohari: Methodology, Software, Writing-Original draft, Sara Sadrneshin: Investigation, Writing, Visualization, Jose J. Diaz: Writing-Review &editing, Supervision, Project administration, Johan Lokk: Conceptualization, Methodology, Software, Validation, Resource, Writing-Review &editing, Supervision, Project administration.

Fig. 2 corticosteroid injection (group I) or within-carpal tunnel corticosteroid injection (group II). A. Needle (N) position in the flexor retinaculum (FR) (group I) with FR thickness of 3.2 before injection. B. Needle and drug infiltration between the FR and median nerve (a group II) (longitudinal view). C. Post-injection FR thickness in a group II patient (longitudinal view). D. Post-injection FR thickness in a group II patient (axial view). Asterisk indicates the mid-canal. (Ra: Radius; LU: Lunate; Ca: Capitate; Sc: Scaphoid; UA: Ulnar Artery)

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